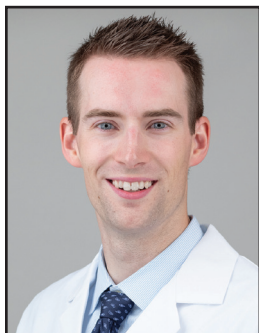


Carol Rees Parrish, MS, RDN, Series Editor

Wilson's Disease: The Copper Connection



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Wilson's disease is a rare genetic disorder in which an inborn error of copper metabolism leads to excess copper accumulation in body tissues and significant organ dysfunction. While long-term prognosis is good in effectively treated patients, its diagnosis and management can be challenging given difficulties interpreting diagnostic testing, issues with medication tolerance and adherence, and restrictive dietary practices. In this setting, patients and clinicians must balance strategies to prevent excessive copper accumulation with ensuring minimal sacrifices to patients' quality of life. This review aims to provide clinicians with a deeper understanding of human copper absorption and metabolism and a practical approach to preventing excess copper accumulation in these individuals.

INTRODUCTION

Wilson's disease (WD), also known as hepatolenticular degeneration, is an autosomal recessive condition first described by Dr. Samuel Alexander Kinnier Wilson in 1912 who noticed a familial clustering of liver disease and neuropsychiatric symptoms. However, it was not until the mid-20th century that the centrality of excessive copper accumulation and effective treatments were discovered.^{1,2} In 1993, our understanding of the disease was revolutionized with identification of mutations in the *ATP7B* gene.^{3,4}

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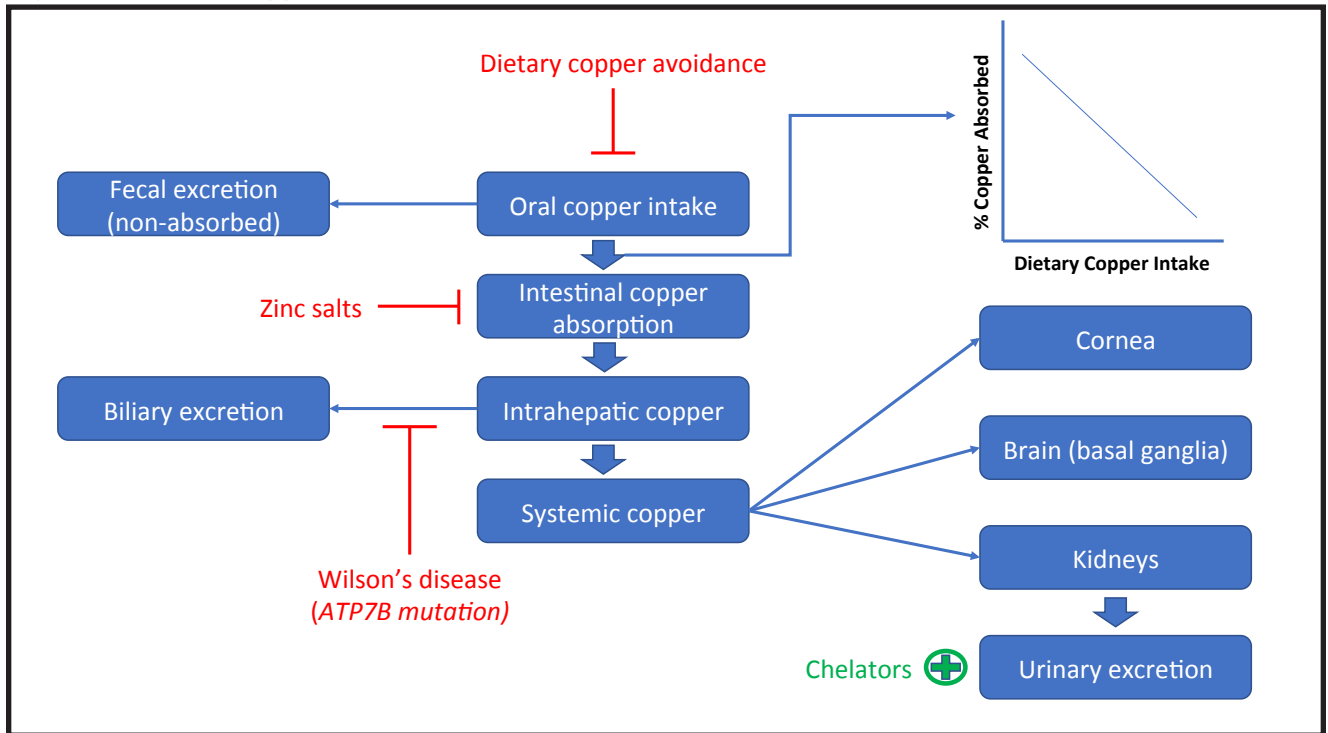
Although WD is rare, with a worldwide prevalence of 10 to 30 per 1 million, approximately 1 in 90 people are carriers of pathogenic *ATP7B* variants.^{3,5,6} Hundreds of specific mutations in this gene have been identified, meaning most affected patients with WD are compound heterozygotes with varying combinations of mutations.^{7,8} Given this genetic diversity, as well as more recent evidence pointing to epigenetic factors, clinical presentations of WD are inhomogenous.⁹

Pathophysiology

Copper is a trace element essential to normal human homeostatic functioning. It has a myriad of roles, including acting as a cofactor for numerous enzymes and helping maintain pigmentation, collagen cross-linking, red blood cell formation, iron absorption, and immune system function.^{10,11} However, in excess, copper can be toxic.

An intricate transport system exists within

Figure 1. Human Copper Metabolism and Effect of Wilson's Disease Treatment



Note: percentage of dietary copper absorbed is inversely proportional to intake

the body to regulate serum levels.⁷ The *ATP7B* gene, located on chromosome 13, encodes a metal-transporting P-type adenosine triphosphate (ATPase). This ATPase is expressed primarily in hepatocytes and facilitates transmembrane transport of copper into bile. In addition, deficient *ATP7B* leads to a failure to incorporate copper into apoceruloplasmin, leading to the characteristic low serum levels of ceruloplasmin seen in WD.³

When mutated, the resulting absence or reduction in ATPase protein production leads to poor excretion of copper into bile. Urinary copper excretion increases in an attempt to compensate, but is less efficient than typical biliary efflux.⁷ Therefore, excess copper accumulates in hepatocytes, causing injury and eventual leakage of copper into the bloodstream, where it can deposit in downstream organs such as the brain, kidneys, and cornea (Figure 1).

Clinical Manifestations

The plethora of variant *ATP7B* alleles lead to varied presentations (Table 1).^{5,7} As an inborn error of metabolism, WD may present *de novo* in either the pediatric or adult population.

Hepatic

In the pediatric population, WD is rarely symptomatic before age five.⁷ Nonetheless, it must be considered in the differential diagnosis of asymptomatic patients older than a year with elevated aminotransferase levels.¹² The latter is the most common presenting feature, however other hepatic manifestations of WD include acute hepatitis, hepatomegaly, cirrhosis (including portal hypertensive-related decompensations), and acute liver failure (ALF).

Neuropsychiatric

Neuropsychiatric manifestations are uncommon before age ten, typically occurring in the second to third decades of life with an average age of onset around 19 years. However, latent onset (up to age 72) has been described.⁷ Subtle signs may include declining academic performance, micrographia, or behavioral changes, with more overt presentations including depression, Parkinson's-like symptoms, dysarthria, and dysphagia.^{7,12}

Ocular

Up to 90% of patients with neuropsychiatric

manifestations develop Kayser-Fleischer (KF) rings, which are caused by copper deposition in the corneal Descemet membrane.^{3,12,13} However, only about half of patients with primarily hepatic disease have KF rings. Another ocular finding is the sunflower cataract, reflecting copper deposits in the lens. Both KF rings and sunflower cataracts do not obstruct vision and improve with treatment. Recurrence suggests non-adherence to therapy.^{3,12}

Other Extrahepatic Findings

WD also has other important extrahepatic manifestations. Perhaps best known is the development of a Coombs-negative hemolytic anemia, which can be the presenting symptom in 7-11% of patients.^{3,12} See Table 1 for a complete listing of findings.

Diagnosis

Major international liver societal guidelines offer slightly different algorithms to establish a diagnosis.^{3,12,14} Slit-lamp examination for KF rings, serum ceruloplasmin, and 24-hour urinary copper excretion are required for initial workup. The combination of KF rings, low ceruloplasmin (<20 mg/dL), and elevated urinary copper excretion (>40 µg/day) is pathognomonic for WD. However, this constellation of findings is frequently absent given the phenotypic variation in WD. Therefore,

adjunctive use of liver biopsy and/or genetic testing may be necessary. Additional features such as the presence of significant liver or neuropsychiatric impairment, Coombs' negative hemolytic anemia, or neuroimaging demonstrating copper deposition in the basal ganglia can be used to support a diagnosis of WD. Nonetheless, careful attention to the inherent limitations of the various testing methods is paramount (Table 2).

Biochemical Liver Tests

Aminotransferases are often mildly elevated in individuals with WD. In the setting of ALF, an alkaline phosphatase to total bilirubin ratio < 4 provides 94% sensitivity and 96% specificity.¹⁵ Interestingly, a low alkaline phosphatase level is uncommon outside of severe presentations.¹⁶

Ceruloplasmin

Measurement of this hepatically synthesized acute phase reactant is fraught with error. Current guidelines suggest that a ceruloplasmin level < 20 mg/dL is consistent with WD, but is only diagnostic when coupled with the presence of KF rings.³ Commercial immunological assays lack discrimination between apoceruloplasmin (lacking copper) and holoceruloplasmin, potentially leading to overestimation of levels and false normal values.^{3,7} In addition, inflammation and

Table 1. Organ-Specific Manifestations of Wilson's Disease

| Organ System | Manifestations |
|-------------------------|--|
| Hepatic | Elevated transaminases, acute hepatitis, hepatomegaly, compensated and decompensated cirrhosis, acute liver failure |
| Neuropsychiatric | Declining academic performance (particularly in the working memory and language domains), micrographia, or behavioral changes, depression, Parkinson's-like symptoms (rigidity, tremor, masked facies), dysarthria, dysphagia, or risus sardonicus (facial musculature contracture producing a sneering grin), autonomic dysfunction, pseudobulbar affect, headache or seizure |
| Ocular | Kayser-Fleischer rings, sunflower cataracts |
| Hematologic | Coombs-negative hemolytic anemia |
| Renal | Fanconi syndrome, nephrolithiasis, acute renal failure |
| Cardiac | Cardiomyopathy, arrhythmia |
| Gastrointestinal | Pancreatitis |
| Musculoskeletal | Arthritis, osteoporosis |
| Dermatologic | Skin changes, nail changes |

hyperestrogenemia can raise ceruloplasmin levels. Conversely, low levels may be seen in *ATP7B* heterozygotes (carriers) or patients with severe renal or enteric protein loss, end-stage liver disease, or inadequate copper supplementation in total parental nutrition.³

Serum Copper

Calculation of non-ceruloplasmin bound copper (the difference between serum copper and three times serum ceruloplasmin) has not been found to accurately distinguish WD from other causes of copper excess (i.e. ALF, chronic cholestasis, copper intoxication). Unfortunately, measurement of this parameter is also limited by overestimation of holoceruloplasmin, leading to a negative and uninterpretable value.^{3,4}

Urinary Copper Excretion

Measurement of 24-hour urinary copper excretion (spot levels are unreliable) can suggest WD, but is not diagnostic on its own. While most symptomatic patients excrete >100 µg/day, 16-23% may excrete less, thus > 40 µg/day is used as a cut-off in most labs. However, patients with autoimmune hepatitis and *ATP7B* heterozygotes can have intermediate to elevated levels.³

Liver Biopsy and Hepatic Copper Content

Biopsy findings often mimic more common liver pathologies. Macrovesicular steatosis may be mistaken for NAFLD and interface hepatitis may falsely suggest autoimmune hepatitis. Identifiable copper by histochemistry is variable and thus unreliable. Ultrastructural tissue analysis can identify pathognomonic mitochondrial abnormalities, but this requires a high degree of *a priori* suspicion for WD.³

Normal hepatic copper content is < 50µg/g dry weight; in WD, levels are typically > 250µg/g. While the latter threshold is relatively specific, an important exception is chronic total parental nutrition (TPN) use, as up to 29% of patients on TPN have high levels of hepatic copper.¹⁷ Intermediate levels may be found in *ATP7B* heterozygotes and patients with chronic cholestatic disease. Therefore, measurement of hepatic copper content should be interpreted in the appropriate context. Additionally, the heterogenous deposition

of copper in WD necessitates high-quality biopsy specimens.³

Genetics

Genetic testing of patients with suspected WD is controversial. A definitive diagnosis of WD can only be made in the presence of two known pathologic alleles. Thus, negative results can decrease, but not exclude, the likelihood of diagnosis given the possibility of unidentified variant alleles. Some authors, and the American Association for the Study of Liver Diseases (AASLD), advocate only for testing in equivocal clinical scenarios.^{3,8} In contrast, both the European Association for the Study of the Liver (EASL) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) advocate for universal genetic testing of suspected individuals.^{12,14} There is consensus, however, among experts and guidelines that first-degree relatives of patients with WD should receive genetic screening.

Treatment

Nutrition

A typical Western diet provides a copper content of 1,400µg/day for adult men and 1,100 µg/day for adult women. In normal health, only 50-120mg of copper is stored in the body, primarily within muscle and bones. As previously mentioned, copper is primarily excreted in bile with smaller amounts excreted in the urine (more if chelation therapy is used), and stool (non-absorbed dietary copper), totaling about 1 mg/day.^{18,19} Presently, the United States Food & Drug Administration (FDA) recommended daily intake of copper is 0.9mg (900µg). However, healthy adult individuals can tolerate up to 10mg daily before sustaining hepatotoxicity.²⁰ Copper deficiency is uncommon in the absence of certain conditions such as gastrectomy or gastric bypass, excessive zinc supplementation or chelator use, Celiac disease, and Menkes disease (an X-linked recessive disorder caused by mutation in the *ATP7A* protein leading to impaired copper absorption).

Dietary guidelines by the major international hepatology societies suggest avoidance of high copper-containing foods (Table 3), particularly during the first year of treatment, as well as consultation with a registered dietitian.^{3,5,14}

Table 2. Limitations of Diagnostic Tests for Wilson's Disease

| Test | Pros | Cons |
|---------------------------------|---|---|
| Physical examination | <ul style="list-style-type: none"> Inexpensive Specific findings (i.e. KF rings, abnormal neuro exam, skin/nail findings) help support diagnosis | <ul style="list-style-type: none"> May be normal (particularly if asymptomatic) No pathognomonic PE findings |
| Biochemical liver tests* | <ul style="list-style-type: none"> Easy to measure Modest transaminase elevations (<2000 IU/mL), low alkaline phosphatase to total bilirubin ratio in acute liver failure are suggestive of WD | <ul style="list-style-type: none"> Mild transaminase elevations non-specific Alkaline phosphatase levels may be normal in non-acute liver failure setting |
| Ceruloplasmin | <ul style="list-style-type: none"> Easy to measure Widely available Very low levels (<5 mg/dL) specific for WD | <ul style="list-style-type: none"> Non-specific (equivocal results in inflammatory conditions, <i>ATP7B</i> heterozygotes, severe renal or liver disease, protein-losing states, poor mineral supplementation of TPN) Overestimation of holoceruloplasmin |
| Serum copper | <ul style="list-style-type: none"> Easy to measure | <ul style="list-style-type: none"> Non-specific (elevations seen in ALF, chronic cholestasis, copper toxicity) Overestimation of holoceruloplasmin |
| 24-hour urinary copper | <ul style="list-style-type: none"> Easy to collect Specific if > 100 µg/day | <ul style="list-style-type: none"> Intermediate levels seen in <i>ATP7B</i> heterozygotes and autoimmune hepatitis Requires special container Spot urine copper not reliable |
| Liver histology (biopsy) | <ul style="list-style-type: none"> Easy to acquire Pathognomonic mitochondrial abnormalities on ultrastructural analysis | <ul style="list-style-type: none"> NAFLD or autoimmune hepatitis can be mimickers Histochemically identified copper unreliable Need high <i>a priori</i> suspicion for WD for ultrastructural analysis to be performed |
| Hepatic copper content | <ul style="list-style-type: none"> Specific if > 250µg/g dry weight | <ul style="list-style-type: none"> Copper deposition heterogenous (prone to sampling error) Confounded by chronic TPN use, chronic cholestasis, <i>ATP7B</i> heterozygotes |
| Genetics | <ul style="list-style-type: none"> Presence of 2 pathologic alleles is pathognomonic | <ul style="list-style-type: none"> Controversial Expensive Possibility of unidentified pathologic alleles |

Avoiding copper-containing foods altogether is difficult for patients and may feel overly restrictive or provoke anxiety.⁶ However, the kinetics of human copper absorption are important for clinicians to understand. Absorption is inversely related to dietary copper content; thus, decreasing proportions of excess copper are absorbed as intake increases, although excretion does not quite match the amount ingested.^{21,22} Therefore, while limiting dietary copper is reasonable, outright avoidance of copper may not be necessary if patients are on appropriate pharmacologic treatment. It is reasonable to fully exclude organ meats (i.e. liver) and shellfish as these have copper contents far exceeding other foods. More recent literature also suggests that a lacto-vegetarian diet may promote both adherence and provide adequate micronutrients, as copper is less bioavailable than in typical omnivorous diets.^{6,23}

Other dietary advice for patients includes avoidance of copper-containing multivitamins, which may contain half to over twice the recommended daily allowance.²⁴ Patients should also avoid ingestion of copper through inorganic sources such as copper cookware and serving dishes. There is a theoretical concern about drinking water run through copper pipes.⁶ However, copper levels in municipal water sources vary greatly and avoidance is generally unnecessary with appropriate dietary modifications and pharmacologic treatment. In those on TPN, copper should be removed. A summary of these nutritional recommendations is available in Table 4.

Antioxidants

Antioxidants, primarily vitamin E, are an area of interest in the treatment of WD; unfortunately, little published data exists.^{25,26} Levels of vitamin E are known to be lower in patients with WD, yet there is no clear correlation between deficiency and clinical symptoms.²⁷⁻²⁹ Further study is warranted although there are currently no registered trials on clinicaltrials.gov.

Zinc Salts

Zinc salts may be used in combination with chelators for synergistic effects or alone as maintenance therapy. Zinc is a competitive inhibitor of copper absorption as it promotes enterocyte synthesis of the

metal chelating peptide metallothionein. The latter protein has a higher binding affinity for copper and therefore this bound copper is eliminated via shed enterocytes into the fecal stream.^{6,30}

Zinc chloride was the first salt utilized, but quickly abandoned given it caused significant gastric irritation.³¹ In 1997, zinc acetate (ZA) was approved by the FDA. This formulation is better tolerated and gastritis may be mitigated by concurrent consumption of a protein-rich snack or meal and use of a proton-pump inhibitor.

The recommended dosing of *elemental* zinc in adults is 50mg three times daily (single daily dosing is insufficient) and should be administered 30 minutes before or 2 hours after a meal. The timing of administration is important as the casein protein in cow's milk and phytates contained in common foods such as corn, cereals, rice, and legumes interfere with zinc absorption.³² Additionally, if treating a pediatric patient less than 50kg, zinc dosing should be reduced to 25mg three times daily. To ensure efficacy (and adherence), clinicians should periodically check a 24-hour urine copper, with values <75µg/day indicating adequacy.^{3,30}

Other zinc salts commonly utilized are zinc sulfate, zinc gluconate (ZG), and zinc picolinate, all of which are available over-the-counter. Some patients have turned to these preparations given intolerance to ZA and/or inadequate prescription insurance coverage. Interestingly, a recent retrospective study of 59 WD patients on zinc salt monotherapy found that half were taking non-prescription zinc. While target 24-hour urine copper levels achieved were highest in patients using ZA, levels were similar with ZG.³⁰ Further head-to-head studies are needed to compare the different salts with respect to their pharmacokinetics and clinical efficacy.

Copper Chelation

Heavy metal chelators have been the mainstay of induction and maintenance therapy and promote urinary excretion of copper. The best-known is *D*-penicillamine, which also has the strongest evidence base for treatment of WD amongst all chelators.^{3,33} However, its use is somewhat limited by significant side effects (Table 5). *D*-penicillamine is also known to induce pyridoxine (vitamin B6) deficiency, which has varied manifestations

Table 3. Copper Content of Selected Foods

| Food | Copper Content | % RDV* |
|--|----------------|--------|
| Beef liver (3oz) | 12.4mg | 1,377 |
| Oysters (3oz) | 4.9mg | 544 |
| Sesame seeds (¼ cup) | 1.5mg | 167 |
| Chocolate, unsweetened (1oz) [†] | 0.9mg | 100 |
| Potatoes, cooked, skin on (1 medium) | 0.7mg | 78 |
| Cashews, dry roasted (1oz) | 0.6mg | 67 |
| Sunflower seeds, toasted (¼ cup) | 0.6mg | 67 |
| Shiitake mushrooms, cooked (½ cup) | 0.6mg | 67 |
| Chickpeas (½ cup) | 0.6mg | 67 |
| Chocolate, dark, 70-85% cacao solids (1oz) | 0.5mg | 56 |
| Tofu, raw, firm (½ cup) | 0.5mg | 56 |
| Avocado, raw (½ cup) | 0.4mg | 44 |
| Spaghetti, whole wheat, cooked (1 cup) | 0.3mg | 33 |
| Salmon, wild Atlantic, cooked (3oz) | 0.3mg | 33 |
| Turkey, ground 85% lean (3oz) | 0.2mg | 22 |
| Asparagus, cooked (½ cup) | 0.1mg | 11 |

Source: NIH Office of Nutritional Supplements Copper Fact Sheet for Health Professionals.

*Recommended Daily Value of 900mcg in non-pregnant or lactating adults

[†]Values vary depending on type of chocolate, with copper content linearly increasing with cocoa percentage

Table 4. Nutritional Recommendations for Patients with Wilson's Disease

- Refer patients to a registered dietitian upon initial diagnosis and PRN basis
- Avoid high copper containing foods (see Table 3); stable patients may incorporate modest amounts of other copper-containing foods under the guidance of their physician and/or dietician
- Avoid copper containing vitamins/mineral supplements
- Remove copper from total parenteral nutrition
- Use non-copper containing cookware and serving dishes
- Zinc supplementation
 - Taken 30 minutes before or 2 hours after meals
 - Adults: 50mg elemental zinc TID
 - Pediatric patients < 50kg, reduce zinc dosing to 25mg TID
- Given a lack of data, antioxidants are not recommended at this time

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including dermatitis, glossitis, angular cheilitis, irritability, neuropathy, and/or depression.³⁴ Supplemental pyridoxine (vitamin B6) is therefore recommended at a dose of 25-50mg/day.^{3,14,23}

An alternative chelator, trientine, is now typically preferred in clinical practice given a more favorable side effect profile.^{3,35-38} Patients and families should be informed, however, that chelator use (particularly *D*-penicillamine) is associated with worsening of neurologic deficits in up to 50% of patients during the induction phase. Unfortunately, the pathophysiology of the aforementioned phenomenon remains poorly understood but stabilizes with time.^{3,7}

Specific dosing for both induction and maintenance is provided in Table 6. Chelators should ideally be administered an hour before or two hours after meals as food interferes with absorption. In stable patients, chelators may be taken closer to mealtime to improve adherence.^{3,14}

Transplantation

Liver transplantation is only necessary in WD patients presenting with ALF or who have developed

decompensated cirrhosis. Severe neurologic disease remains a controversial indication.³⁹ Excellent outcomes have been achieved in heterogenous cohorts of both pediatric and adult patients, with 1-year, 5-year, and 10-year survival rates of 79-88%, 73-83%, 60-87% respectively.^{40,41}

Monitoring

There is little consensus regarding monitoring parameters and current guidelines are based upon expert opinion. In general, patients starting pharmacologic therapy should be monitored at least weekly (particularly if using chelators given the risk of neurologic deterioration) while titrating dosages, with less frequent visits as remission is achieved. Physical exam, complete blood count, biochemical liver tests, and 24-hour urine copper form the basis of this assessment. Initially, when chelation is used, urinary copper excretion should be significantly elevated, often >1000 µg/day during induction and then fall to between 200-500 µg/day in the maintenance phase. Levels below 200 µg/day indicate either nonadherence or overtreatment and induction of copper deficiency.⁴² If zinc monotherapy is used, urinary copper

Table 5. Side Effects of Commonly Utilized Medications for Wilson's Disease

| D-penicillamine | Trientine | Zinc Salts |
|--|--|--|
| <ul style="list-style-type: none"> • Sensitivity reaction (first 1-3 weeks) • Ageusia • Arthralgias • Lupus-like reaction • Bone marrow suppression • Sideroblastic anemia • Nephrotoxicity • Skin changes (progeria, elastosis perforans serpingosa, pemphigus, lichen planus, aphthous stomatitis) • Serous retinitis • Hemosiderosis • Myasthenia gravis • Polymyositis • Goodpasture syndrome (rare with current doses) | <ul style="list-style-type: none"> • Gastritis • Sideroblastic anemia • Aplastic anemia (rare) • Lupus-like reaction • Arthralgias • Muscle cramps | <ul style="list-style-type: none"> • Gastritis • Biochemical pancreatitis (asymptomatic) • Iatrogenic copper deficiency (anemia, neutropenia, sensory and/or motor neuropathies and myelopathies) |

Table 6. Dosing of Chelators in Adult Patients with Wilson's Disease

| | D-penicillamine | Trientine |
|--------------------------|--|--|
| Induction Phase | Dosing: 250-500 mg/day, increased by 250mg Q4-7 days to maximum of 1000-1500mg daily in 2-4 divided doses. Should be administered 1h before or 2h after meals. Adjunctive: pyridoxine (vitamin B6) 25-50mg/day Length: 4-6 months | Dosing: 20 mg/kg daily in 2-3 divided doses (not to exceed 1500 mg/day). Should be administered 1h before or 2h after meals. Adjunctive: no pyridoxine (vitamin B6) needed Length: 4-6 months |
| Maintenance Phase | Dosing: 750-1000 mg/day in two divided doses Length: indefinite until transplant or switch to zinc monotherapy in stable patients | Dosing: 15 mg/kg in 2-3 divided doses* Length: indefinite until transplant or switch to zinc monotherapy in stable patients |

*A small study showed efficacy with 20 mg/kg daily dosing for easier adherence⁴⁵

excretion should be $<75 \mu\text{g/day}$.^{3,12} Annual slit-lamp exams are recommended to ensure either recession or absence of KF rings to document therapeutic adequacy and adherence.¹²

Bone mineral density has also been shown to be severely reduced in children with WD, although it may stabilize with prompt treatment. However, it appears this skeletal abnormality is independent of vitamin D levels, as a small case-control study demonstrated similar serum 25-hydroxy vitamin D in both control and WD patients.⁴³ Obtaining a baseline DEXA scan at presentation and after a year of therapy may be helpful to quantify the degree of demineralization and ensure stability.

CONCLUSION

WD is a rare but important cause of liver disease with many extrahepatic manifestations. Its complex genetics yield a spectrum of phenotypes seen in clinical practice. While untreated disease can lead to end-stage liver disease and devastating neurological consequences, timely identification and treatment is generally associated with a good prognosis.⁴⁴ In symptomatic patients, chelation alone or in combination with zinc salts decreases systemic copper load rapidly. Maintenance therapy with zinc salts alone, particularly the ZA or ZG formulations, may be feasible and has a better side

effect profile than chronic chelator use.

Although physicians may reference current societal guidelines when discussing nutritional treatment plans with their patients, the more practical approach to specific dietary guidance contained within this review is vital to patient satisfaction and treatment success. ■

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Answers to this month's crossword puzzle:

